# Respiratory Carcinogenicity Assessment of Soluble Nickel Compounds

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**The many chemical forms of nickel differ in physicochemical properties and biological effects. Health assessments for each main category of nickel species are needed. The carcinogenicity assessment of water-soluble nickel compounds has proven particularly difficult. Epidemiologic evidence indicates an association between inhalation exposures to nickel refinery dust containing soluble nickel compounds and increased risk of respiratory cancers. However, the nature of this association is unclear because of limitations of the exposure data, inconsistent results across cohorts, and the presence of mixed exposures to water-insoluble nickel compounds and other confounders that are known or suspected carcinogens. Moreover, well-conducted animal inhalation studies, where exposures were solely to soluble nickel, failed to demonstrate a carcinogenic potential. Similar negative results were seen in animal oral studies. A model exists that relates respiratory carcinogenic potential to the bioavailability of nickel ion at nuclear sites within respiratory target cells. This model helps reconcile human, animal, and mechanistic data for soluble nickel compounds. For inhalation exposures, the predicted lack of bioavailability of nickel ion at target sites suggests that water-soluble nickel compounds, by themselves, will not be complete human carcinogens. However, if inhaled at concentrations high enough to induce chronic lung inflammation, these compounds may enhance carcinogenic risks associated with inhalation exposure to other substances. Overall, the weight of evidence indicates that inhalation exposure to soluble nickel alone will not cause cancer; moreover, if exposures are kept below levels that cause chronic respiratory toxicity, any possible tumor-enhancing effects (particularly in smokers) would be avoided.** ***Key words:*** **cancer, epidemiology, mechanism, nickel, risk assessment.** *Environ Health Perspect* **110(suppl 5):841–844 (2002).**
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Inhalation of high concentrations of certain nickel-containing dusts in past nickel refining operations has been associated with increased respiratory cancer risks (*1*). However, the presence of mixed exposures to various chemical species of nickel (*2*) as well as other confounders made it difficult to identify the carcinogenic nickel species based on the epidemiologic data. Animal inhalation studies have confirmed the carcinogenicity of certain nickel compounds (e.g., nickel subsulfide, high-temperature nickel oxide) but failed to indicate any carcinogenic potential for a water-soluble nickel compound (nickel sulfate hexahydrate) (*3*).

The different physicochemical properties and biological effects among categories of nickel compounds suggest that health assessments for each of these categories are needed. The carcinogenicity assessment of water-soluble nickel compounds has proven to be particularly difficult. This can be illustrated by reviewing the carcinogenicity listing decisions of several organizations within the last few years. In 1998, the U.S. National Toxicology Program (NTP) began consideration of the proper carcinogenicity classification for all categories of nickel compounds. This was part of the process leading to a possible revision of the listing of these compounds in the NTP's *Ninth Report on Carcinogens* (*4*). During their discussions, the NTP Review Groups 1 and 2 as well as its Board of Scientific Counselors subcommittee voted to list "all nickel compounds" (including soluble nickel compounds) as "known to be human carcinogens" (*1*) (the listing recommendation has not yet been made final through publication in the *Report on Carcinogens*). That same year, the American Conference of Governmental Industrial Hygienists published revised threshold limit values for the main categories of chemical nickel species and assigned to them different carcinogenic classifications. Although nickel subsulfide and water-insoluble nickel compounds were classified as category A1 (confirmed human carcinogen), water-soluble nickel compounds received a category A4 classification (not classifiable as a human carcinogen) (*5*). Similar contrasting assessments were made the following year. In 1999, Beraterkreis Toxikologie in Germany recommended a category C1 classification (substances known to be carcinogenic to man) for water-soluble nickel compounds (*6*), whereas the Toxicological Excellence in Risk Assessment group conducting a risk assessment for Health Canada, U.S. Environmental Protection Agency, and the Metal Finishers Association of Southern California concluded that the "carcinogenicity of soluble nickel compounds cannot be determined" (*7,8*).

The main reason for these discrepancies lies in the contradictory findings provided by the epidemiologic, animal and *in vitro* genotoxicity data. Without a unifying mechanism that can account for these discrepancies and integrate them into a single model for nickel respiratory carcinogenesis, the assessments will continue to vary widely depending on whether more emphasis is given to the human or the animal data and how these data are interpreted.

In this article, the main features of the epidemiologic data pertaining to soluble nickel compounds are presented. Based on the human data, two possible hypotheses about the carcinogenic potential of soluble nickel compounds are considered. The animal and *in vitro* data for soluble nickel compounds are briefly reviewed, evaluating their consistency with the possible hypotheses. A model for the respiratory carcinogenicity of nickel compounds is briefly reviewed and the predicted carcinogenic potential for soluble nickel compounds based on this model is considered. Finally, an assessment of carcinogenicity of soluble nickel compounds based on the weight of evidence from the human, animal, and mechanistic data is presented. This review is not meant to be exhaustive and in some cases only representative references are cited.

## Human Data

Human epidemiologic evidence has indicated an association between increased risk of respiratory cancers and inhalation exposures to refinery dust containing a mixture of water-soluble and water-insoluble nickel compounds (*1,9–11*). Soluble nickel (Ni) exposures appear to increase respiratory cancer risks at lower exposure concentrations (>1 mg Ni/$m^3$ workplace dust) than more water-insoluble nickel compound exposures (>10 mg Ni/$m^3$ workplace dust) (*1*). However, the ability of epidemiologic studies to determine whether soluble nickel compounds had a causal role or rather an enhancing role on the observed excess tumor incidence is limited by the poor quality of existing exposure data, inconsistent results across cohorts, and the presence of mixed exposures to water-insoluble nickel compounds (e.g., sulfidic and oxidic nickel compounds) and other confounders with known or suspected carcinogenic potential (e.g., soluble cobalt compounds, arsenic, acid mists, polycyclic aromatic hydrocarbons, cigarette smoke, etc.). Standard mortality ratios among groups of workers are less consistent across cohorts with predominantly soluble nickel exposures

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than across cohorts with predominantly insoluble nickel exposures. Moreover, there is no consistent dose response with increasing concentrations of soluble nickel (*1*). A recent update of one of these cohorts has indicated a synergistic response between exposure to nickel compounds and cigarette smoking in the induction of lung tumors (*10*). A study of nickel platers exposed to predominantly soluble nickel compounds (no sulfidic or oxidic nickel exposures) did not show increased respiratory cancer risks (*12*). Unfortunately, the small size of the cohort and the relatively low exposure levels diminish the power of the nickel platers' study to conclusively evaluate the carcinogenic potential of soluble nickel compounds.

Therefore, from the human data alone, two hypotheses can be derived, that soluble nickel compounds either *a*) are respiratory carcinogens with greater potency than any of the water-insoluble nickel compounds (e.g., nickel subsulfide) or *b*) are not complete carcinogens, but at exposure levels that result in chronic respiratory toxicity, they can enhance the respiratory carcinogenicity associated with concurrent inhalation exposures to carcinogens.

Given that water-soluble nickel compounds are more toxic by inhalation than insoluble ones, both hypotheses are consistent with increased respiratory cancer risks seen at lower exposure levels of soluble (>1 mg Ni/$m^3$) than insoluble (>10 mg Ni/$m^3$) nickel compounds.

## Animal Data

Well-conducted inhalation studies in rats and mice, where exposures were solely to nickel sulfate hexahydrate, failed to demonstrate a carcinogenic potential for this compound (*3*). Similar negative results were seen in animal studies through oral exposure (*13–15*) and intramuscular injection studies with soluble nickel compounds alone (*16–19*). One transplacental carcinogenicity study in rats with soluble nickel alone showed significant induction of pituitary tumors in offspring of exposed rats (*20*). However, the doses used in this study were highly toxic to the mothers and may have resulted in abnormal hormonal imprinting of the fetuses. Pituitary tumors can occur as a consequence of hormonal disruption in the rat (*21*). This finding was not reproduced in any of the other studies done with soluble nickel or in another transplacental carcinogenicity study conducted with nickel subsulfide (*22*), raising doubts about the relevance of this study for evaluating human carcinogenic potential.

Interestingly, oral or injection animal studies in which soluble nickel was administered in combination with a carcinogen suggest a possible tumor-enhancing effect that manifests in the kidney, the target organ for systemic nickel toxicity (*23,24*). Again, the results suggest that chronic toxicity induced by soluble nickel can, under certain circumstances, result in enhancement of tumorigenicity of carcinogenic substances.

Rat inhalation studies are very important to evaluate the human respiratory carcinogenic potential of nickel compounds. Rats are a nickel-responsive species (tumors can be induced by inhalation of nickel subsulfide and green nickel oxide), and inhalation studies are the only studies that take into account all the factors that contribute to the bioavailability of nickel at nuclear sites of target cells in the respiratory tract. Therefore, it is worth addressing some design issues regarding the negative NTP nickel sulfate hexahydrate study (*3*).

It has been suggested by some groups that the highest concentration used in the rat 2-year cancer bioassay [0.1 mg Ni/$m^3$; mass median aerodynamic diameter (MMAD), 2.2 μm] was below the maximum tolerated dose and that if a higher concentration had been tested, a positive tumorigenic response might have been found. As is typical, the 2-year bioassay concentrations were selected based on the results from the subchronic studies, and those results showed similar toxicities for 0.1 mg Ni/$m^3$ of nickel sulfate hexahydrate or nickel subsulfide. Nevertheless, the tumorigenic responses were quite different, with a positive response for lung tumor induction for nickel subsulfide and a negative response for nickel sulfate [see discussion of this issue by Haber et al. (*7*)]. In addition, the use of higher doses of nickel sulfate would have been precluded if the dose response for whole-animal toxicity (i.e., mortality) in rats were very steep. In a recent subchronic study designed to expose rats to 0.4 mg Ni/$m^3$ (MMAD, 1.9 μm) for 13 weeks, 12 of 39 rats (31%) died during the second week of exposure (*25*). The highest concentration was then reduced to 0.2 mg Ni/$m^3$, and new animals were added to the study. These toxicity results confirm a steep dose response for toxicity/mortality and indicate that for a 2-year study (rather than a 13-week exposure period), a concentration below 0.2 mg Ni/$m^3$ would need to be selected. Otherwise, decreased survival would diminish rather than increase the chances of detecting tumors with reasonable power. Therefore, these results confirm that the 0.1 mg Ni/$m^3$ highest exposure level used in the 2-year NTP bioassay was indeed at or near the maximum tolerated dose.

It also has been noted that the highest concentration to which rats were exposed in the NTP bioassay was 0.1 mg Ni/$m^3$ (MMAD, 2.2 μm), whereas workers showing excess respiratory cancer risks experienced soluble nickel exposures above 0.1 mg Ni/$m^3$ (workplace dust). Some have suggested that this difference in exposure levels could explain why rats did not get tumors whereas some workers did. In considering this point, it is important to note that the aerosol used in the NTP studies had particles of a MMAD of 2.2 μm. In contrast, the particle size distribution of the aerosols in the workplace is broader and characterized by coarser particles (e.g., MMAD > 30–50 μm). Particles in the 2 μm range comprise less than 10% of the workplace dust. Therefore, for a proper comparison between animal and human exposures, the particle size of the aerosols as well as deposition/clearance differences between animals and humans must be taken into consideration. An animal-to-human extrapolation study based on deposition/clearance models for rat and human lungs allows calculation of equivalent exposures (*26–28*). These results indicate that after accounting for particle size distribution, the soluble nickel exposure levels that did not induce tumors in rats are indeed equivalent (in terms of nickel lung burden) to those experienced by workers in the nickel refinery epidemiologic studies (Figure 1) [see further discussion of this issue by Haber et al. (*7*)].

In summary, the weight of evidence based on the animal data argues against hypothesis (*a*) that soluble nickel compounds by themselves are carcinogens of higher potency than water-insoluble nickel compounds. Rather, it supports hypothesis (*b*) that soluble nickel compounds by themselves are not carcinogenic but that at concentrations above those that result in chronic respiratory toxicity, they may enhance the carcinogenicity of simultaneous inhalation exposure to carcinogens.

## *In Vitro* Studies

*In vitro*, soluble nickel compounds induce essentially the same genotoxic effects as water-insoluble nickel compounds (e.g., nickel subsulfide) but with lower potency (*29–31*). The higher concentrations required to see these effects with soluble nickel compounds are attributed to the less efficient cellular uptake of $Ni^{2+}$ ion from soluble than from insoluble nickel compounds. For example, the percentages of nickel in the nucleus of Chinese hamster ovary cells exposed to nickel sulfide/subsulfide are up to 300- to 500-fold higher than the percentage levels of $Ni^{2+}$ in the nucleus of cells exposed to equivalent levels of nickel chloride (*32,33*).

*In vitro* results indicate a potential for soluble nickel compounds to cause genotoxic effects (when sufficient amounts reach the cell nucleus) and, in that respect, are consistent with a possible carcinogenic effect of soluble nickel compounds [hypothesis (*a*)]. However, based on the *in vitro* results, soluble nickel compounds would be expected to have a much lower carcinogenic potency than insoluble nickel compounds, which is inconsistent with the human data. The *in vitro* results also are consistent with hypothesis (*b*) discussed above (soluble nickel compounds by themselves are not carcinogenic) when the differences between *in vitro* and *in vivo* exposures are

taken into account. Specifically, there are active clearance mechanisms *in vivo* that are absent in a petri dish. Because there is no clearance, prolonged *in vitro* exposures to soluble nickel compounds at high enough levels eventually allow some $Ni^{2+}$ ion to reach the cell nucleus. *In vivo*, however, this is precluded by the rapid lung clearance that has been observed in experimental animals and humans (*3,34,35*). To achieve sufficiently high concentrations of $Ni^{2+}$ ion at respiratory tract target sites would require animals to be exposed to concentrations that likely would result in severe toxicity and death. In summary, results from *in vitro* studies tend to favor hypothesis (*b*), although hypothesis (*a*) cannot be totally disregarded based solely on *in vitro* data.

Research conducted in the last few years has focused on the effects of nickel ions on gene expression [see review by Salnikow and Costa (*36*)]. *In vitro* exposure of certain cell types to specific concentrations of nickel compounds has been shown to affect the levels of thrombospondin 1 and hypoxia-inducible transcription factor-1 (HIF-1) (*37,38*). Induction of yet another set of proteins such as Cap43 (yet unknown function), vascular endothelial growth factor, plasminogen activator inhibitor-1, and erythropoeitin seems to be mediated by the effects of nickel on HIF-1 (*39–42*). These signal transduction effects appear to be independent of the genotoxic (nuclear) effects of nickel because they can be equally elicited by both soluble and insoluble nickel compounds. These nickel-induced changes in gene expression could play a role in the *in vivo* tumorigenicity and/or tumor enhancement effects seen with nickel compounds. Animal studies are now needed to evaluate whether some of these *in vitro* effects are related to site-specific carcinogenic effects, site-specific toxic effects, or even possible homeostatic functions of nickel ions.

## Respiratory Model for Nickel Carcinogenesis

Even though some changes in gene expression may be elicited at the cell membrane level, many of the nickel effects associated with cell transformation and carcinogenesis depend on the presence of nickel in the cell nucleus (*35*). A model for nickel carcinogenesis can be based on the assessment of the bioavailability of nickel ion at nuclear sites of respiratory target cells (*7,43–45*). This model predicts that it is not just the presence of nickel in a given inhaled substance that determines its carcinogenic potential but rather whether this nickel is bioavailable in sufficient amounts at nuclear sites of epithelial cells to result in respiratory tumor induction. The factors that influences this bioavailability and thus the intrinsic hazard of a substance include particle size, surface characteristics, mechanism of clearance from the respiratory tract, mechanism of uptake into target cells, respiratory and whole animal toxicity, and solubility (relative ease of $Ni^{2+}$ ion release) (Figure 2).

The particle size of the inhaled dust not only will affect respiratory tract deposition but also will influence clearance of the particles and uptake into target cells (*46*). Surface area and surface charge also may affect clearance mechanisms and uptake by target cells (*47*). Uptake of water-insoluble nickel particles via phagocytosis is an efficient mechanism to deliver nickel to target cells, whereas uptake of nickel ions derived from soluble nickel compounds (or from dissolution of more insoluble compounds outside the cells) is not (*48*). $Ni^{2+}$ ion release rates from water-insoluble nickel compounds inside the cells also influence the bioavailability of $Ni^{2+}$ ion derived from dissolution of phagocitized particles at nuclear sites (*33*). Water solubility of inhaled nickel compounds appears to be directly related to whole animal toxicity and to some extent to respiratory toxicity as well (*3,34*).

As a result of these interactions, the nickel species that have the greatest potential to induce tumors are those that *a*) are insoluble enough to be present in the lung as particles, *b*) can get into epithelial cells via phagocytosis, and *c*) once inside the phagosomes, release high levels of $Ni^{2+}$ ion (*49*). An example of such a compound is nickel subsulfide. This compound is partially soluble in biological fluids and is taken up by cells with ease. Inside the cells, because of the acidic pH of phagosomes, high levels of nickel ions are released and delivered to nuclear sites. In addition, its partial solubility in biological fluids results in relatively high levels of respiratory toxicity, with increased cell proliferation (*25*) that may contribute to tumor formation. For this compound, the human and animal data consistently indicate a respiratory carcinogenic potential and confirm the genotoxic effects seen in *in vitro* studies. Most organizations are in agreement in classifying nickel subsulfide as a known human carcinogen.

By contrast, water-soluble nickel compounds immediately dissociate into $Ni^{2+}$ ions and counter ions upon inhalation. Uptake of $Ni^{2+}$ ions into the cells is very inefficient and further impaired by the rapid clearance of $Ni^{2+}$ ions from the lung and the high-affinity binding of $Ni^{2+}$ ions to proteins (*45*). This model predicts that soluble nickel compounds should have much lower carcinogenic potency than water-insoluble nickel compounds. In theory, if the inhaled concentrations of soluble nickel compounds were high enough, sufficient

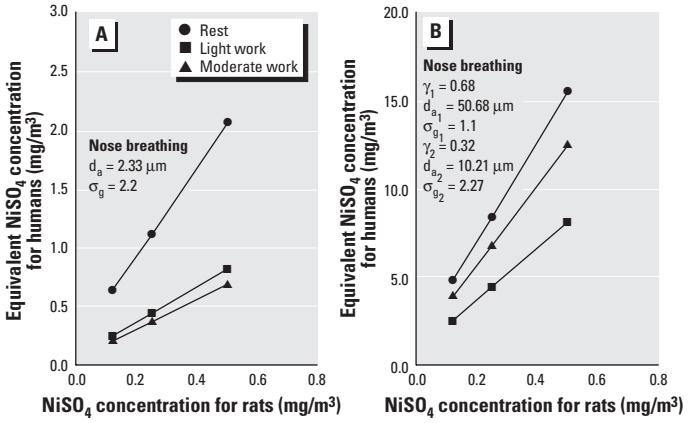


**Figure 1.** Equivalent rat and human exposure levels to nickel sulfate ($NiSO_4$) hexahydrate that result in similar nickel lung burdens using a deposition/clearance model developed by Yu and colleagues (*26,28*). Abbreviations: $d_a$, particle aerodynamic diameter; $\sigma_g$, geometric standard deviation; $\gamma_1$, fraction of particles with $d_{a_1}$ and $\sigma_{g_1}$; and $\gamma_2$, fraction of particles with $d_{a_2}$ and $\sigma_{g_2}$. (*A*) Considers the human aerosol as having the same particle size distribution as the animal aerosol ($d_a$ = 2.3 µm). (*B*) Considers the real workplace size distribution of the human aerosol rather than the one in the animal aerosol.

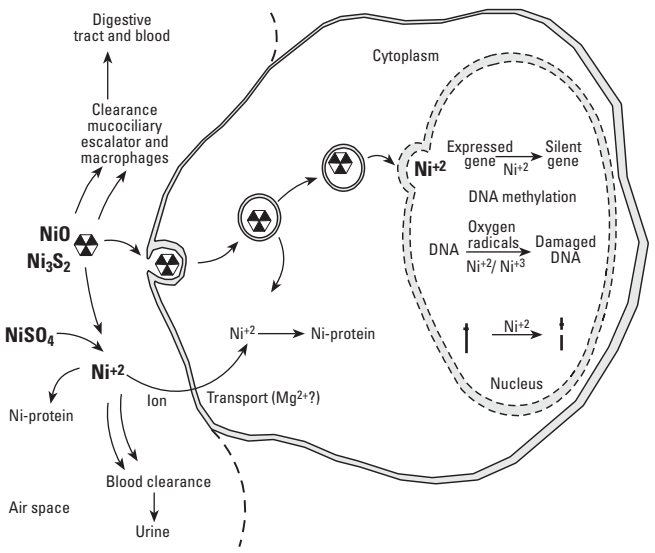


**Figure 2.** Interactions of nickel compounds with epithelial (target) cells in the bronchioalveolar region of the lung. Modified from Oller et al. (*45*).

$Ni^{2+}$ ion should reach the nucleus of target cells. In practice, however, this is not possible because of the toxicity of the $Ni^{2+}$ ion that results in high animal mortality at concentrations below those required for a tumorigenic effect (*3*). Therefore, inhalation of soluble nickel compounds does not result in sufficiently high bioavailable nickel at nuclear target sites to induce tumors. However, as discussed for nickel subsulfide, soluble nickel compounds can cause respiratory toxicity and may enhance the carcinogenicity of other compounds, perhaps through some of the recently identified cell signaling pathways (*36*).

As discussed above, only inhalation studies can be used to ascertain the respiratory carcinogenic potential of nickel-containing substances because only inhalation studies take into account all the factors that influence $Ni^{2+}$ ion bioavailability and carcinogenic potential. In summary, mechanistic information supports hypothesis (*b*) (i.e., soluble nickel compounds by themselves are not carcinogenic but that at concentrations above those that result in chronic respiratory toxicity they may enhance the carcinogenicity of inhalation exposure to carcinogens).

## Overall Assessment of Carcinogenicity

The weight of evidence from the combined analysis of human, animal, and *in vitro* data considered within the current model of respiratory carcinogenicity of nickel indicates that inhalation of soluble nickel compounds (alone) is not expected to result in human carcinogenicity. However, the human and animal data suggest that at concentrations that result in chronic toxicity, soluble nickel compounds may enhance the tumor response elicited by inhalation of carcinogens such as nickel subsulfide or cigarette smoke. Further support for this assessment comes from using animal inhalation data (in which chronic lung inflammation is considered a surrogate for tumor-enhancing effects) to extrapolate respiratory cancer risks for humans. The calculated risks, based on the assumption that any possible respiratory tumor-enhancing effect of soluble nickel is due to chronic respiratory toxicity, are in general agreement with the risks observed in epidemiologic studies (*50*).

Different hazard identification programs employ different (although generally similar) criteria to classify substances as carcinogens. In any of these programs, however, one would not expect a chemical that by itself does not cause cancer to be classified as a known human carcinogen. Within each classification system, the proper label for substances that by themselves are demonstrated not to be carcinogens (in sensitive animal species) but may at high enough concentrations enhance the carcinogenic risk associated with inhalation exposure to other substances will need to be considered. This has important implications in terms of risk assessment because it suggests that if exposures to soluble nickel compounds are kept below the levels that cause chronic respiratory toxicity, any possible tumor-enhancing effects (particularly in smokers) would be avoided.

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